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EXAMINER	
TUNGATURTHI, PARITHOSH K	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/719,006	HORI ET AL.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6.22.06;9.13.04;*8.13.04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-23 have been cancelled.

2. Claims 24-38 are under examination.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 24-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 24 and 29 are not clear for reciting ".....wherein the first and second amplifiable markers are amplified by the same amplification agent...", because the exact meaning of the phrase "same amplification agent" is not clear. The specification lacks information as to what the applicant means by "same amplification agent". There is no information in the disclosure as to what an amplification agent is and further what amplification agents are used. Does that applicant mean that the step comprises a certain agent that can amplify both the markers? According to the definition (by Merriam-Webster Dictionary), an amplification agent is any compound (DNA, RNA, protein, peptide, etc) that is involved in massive replication of genetic material and especially of a gene or DNA sequence (as in a polymerase chain reaction). Hence, as written, the claims are unclear as to what "same amplification agent" means. Does that mean both markers are cloned into similar vectors such that they are under

the control of the same promoters and same origin of replication? As written, the claims are confusing and appropriate correction is requested from the applicant.

For the purposes of this office action, the claims are interpreted as such the "same amplification agent" is referred to as such that the cloning vectors are under the control of same promoters and same origin of replication, such that the same agents or chemicals can be used to initiate the transcription of such vectors for an effective and efficient amplification of genes to produce the proteins of interest; in this instant, antibody heavy or light chains.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 24-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing a human antibody, said method comprising: (a) introducing a first polynucleotide into a first mammalian myeloma cell, wherein the first polynucleotide comprises a first amplifiable marker and a sequence encoding a heavy chain polypeptide of a human antibody; (b) introducing a second polynucleotide into a second mammalian myeloma cell, wherein the second polynucleotide comprises a second amplifiable marker and a sequence encoding a light chain polypeptide of the said human antibody; (c) culturing each of said first and second mammalian myeloma cells separately in the presence of an amplification agent, wherein the first and second amplifiable markers are amplified by the same amplification agent;

and (d) fusing the cultured cells produced by steps (a)-(c) to form a hybrid cell, wherein the hybrid cell expresses the said human antibody, does not reasonably provide enablement for producing a human antibody, said method comprising:..... a sequence encoding a heavy chain polypeptide of a human antibody..... a sequence encoding a light chain polypeptide of the ANY human antibody..... wherein the hybrid cell expresses the ANY human antibody.. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a method for producing a human antibody, said method comprising: (a) introducing a first polynucleotide into a first mammalian myeloma cell, wherein the first polynucleotide comprises a first amplifiable marker and a sequence encoding a heavy chain polypeptide of a human antibody; (b) introducing a second polynucleotide into a second mammalian myeloma cell, wherein the second polynucleotide comprises a second amplifiable marker and a sequence encoding a light chain polypeptide of the ANY human antibody; (c) culturing each of said first and

second mammalian myeloma cells separately in the presence of an amplification agent, wherein the first and second amplifiable markers are amplified by the same amplification agent; and (d) fusing the cultured cells produced by steps (a)-(c) to form a hybrid cell, wherein the hybrid cell expresses the ANY human antibody, in addition to the limitations as listed in the instant claims.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. Although biotechnology has made great strides in the recent past, these references serve to demonstrate exactly how little we really know about the art. For example, Rudikoff et al (Proc. Natl. Acad. Sci. USA 1982 Vol 79 page 1979) teach that even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRS, may dramatically affect antigen-binding function. Rudikoff et al. also teach that the alteration phosphocholine-binding function of a single amino acid in the CDR of a myeloma protein resulted in the loss of antigen-binding (please see the entire document, in particular)

Further, Colman et al (Research in Immunology 1994, 145:33-36) teach the specificity of antibody-antigen interaction, wherein in one structural context, a very conservative substitution may abolish binding; in another, a non-conservative substitution may have very little effect on the binding affinity. Current estimated of the potential number of antibody molecules that can be generated by all the known genetic mechanisms is in excess of 10^{18}. This and similar other estimates assume each of the 20 amino acids is different from every other amino acid, which is appropriate for

purpose of enumeration but not for the purpose of estimating how many different antibody specificities can be produced by an animal (page 35, in particular).

In addition, Ibragimova and Eade (Biophysical Journal, Oct 1999, Vol. 77, pp. 2191-2198) teach that factors affecting protein folding and stability are governed by many small and often opposing effects and that even when the "rules" are know for altering the stability of a protein fold by the introduction of a single point mutation the result is not reliable because the balance of forces governing folding differs for different protein sequences, and that the determination of the relative magnitude of the forces governing the folding and stability of a given protein sequence is not straightforward (page 2191, first column, lines 12-17 and second column, lines 3-8).

These results demonstrate that the heavy and light chain expression as claimed in the instant claims have to be of the same antigen specificity. For example, if the first myeloma cell consists of a polynucleotide encoding a heavy chain polypeptide of one human antibody, the second myeloma cell must consist of a polynucleotide encoding the light chain polypeptide of same human antibody, and not any other light chain in order to result in a antigen binding, functional antibody.

In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of derivatives encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

6. Claims 24, 25, 27-32 and 34-38 rejected under 35 U.S.C. 102(b) as being anticipated by Trill et al (Current Opinion in Biotechnology. 1995. 6:553-560; IDS – 06/22/2006) as evidenced by Orlandi et al (Proc. Natl. Acad. Sci. USA, 86:3833-3837, 1989).

The instant claims are drawn to a method for producing a human antibody, said method comprising: (a) introducing a first polynucleotide into a first mammalian myeloma cell, wherein the first polynucleotide comprises a first amplifiable marker and a sequence encoding a heavy chain polypeptide of a human antibody; (b) introducing a second polynucleotide into a second mammalian myeloma cell, wherein the second polynucleotide comprises a second amplifiable marker and a sequence encoding a light chain polypeptide of the said human antibody; (c) culturing each of said first and second mammalian myeloma cells separately in the presence of an amplification agent, wherein the first and second amplifiable markers are amplified by the same amplification agent; and (d) fusing the cultured cells produced by steps (a)-(c) to form a hybrid cell, wherein the hybrid cell expresses the said human antibody, recovering the multi-component

protein from the hybrid cell, wherein the first and second cell are NSO cells, wherein the first and second amplifiable markers are each DHFR, glutamine synthetase, or adenosine deaminase; in addition to a method for producing a human antibody, said method comprising: (a) culturing a first recombinant mammalian myeloma cell in the presence of a first amplification agent to produce a first amplified recombinant cell; wherein the first cell comprises a first polynucleotide comprising a first amplifiable marker and a sequence encoding a heavy chain polypeptide, (b) culturing a second recombinant mammalian myeloma cell in the presence of a second amplification agent to produce a second amplified recombinant cell; wherein the second cell comprises a second polynucleotide comprising a second amplifiable marker and a sequence encoding a light chain polypeptide, wherein the first and second amplifiable markers are amplified by the same amplification agent; and (c) fusing the first and second amplified recombinant mammalian myeloma cells to form a hybrid cells, wherein the hybrid cell expresses a human antibody; wherein a human antibody is produced, additionally recovering the antibody from the hybrid cell, wherein the first and second cell are NSO cells, wherein the polynucleotide encoding the heavy chain polypeptide and the polynucleotide encoding the light chain polypeptide are obtained from a B-cell or a hybridoma cell, wherein said B-cell or hybridoma cell produce an antibody, wherein the first and second cells expressing the desired heavy and light chains are selected for on or more desirable characteristics prior to fusing, wherein the desirable characteristic is a high production rate, and wherein the first and second amplifiable markers are each DHFR, glutamine synthetase, or adenosine deaminase.

Trill et al teach the production of monoclonal antibodies in COS and CHO cells, in particular genetically engineered human antibodies (abstract, in particular). Trill et al teach vectors for the expression of mABs in COS and CHO cells (figure 1, in particular). Trill et al teach a mammalian cell comprising the polynucleotide encoding a heavy chain polypeptide of a human antibody and a mammalian cell comprising the polynucleotide encoding a light chain polypeptide of a human antibody, in addition to amplifiable markers, for example "DHFR" for heavy chain and "neo" for light chain. In addition, Trill et al teach there are numerous reports that describe the use of vector system in which the two Ig chains are situated in different plasmids containing independent amplifiable/selectable markers (as illustrated in figure 1 page 554, for CHO cells). Trill et al teach the construction of the heavy and light chain genes with the different markers, such as DHFR and neo, under the control of constitutively expressing simian virus (sv40) T-antigen, and, therefore, support replication of expression plasmids containing the SV40 origin of replication, amplifying the introduced expression cassettes (page 554, first column in particular). Trill et al teach that typically the heavy-chain and light-chain immunoglobulin expression cassettes utilized in the COS system are similar to those used to generate stable CHO lines with the expression plasmids carry the SV40 origin of replication, indicating that both the vectors are under the control of same amplification system. The instant application discloses the cassette includes for example, appropriate antibody genes, a gene amplification system, and an HPRT selectable marker (paragraph 65, in particular). Thus, it is inherent that the amplification system utilized by Trill et al utilizes the same amplification agent (please see the

paragraph 4 above), as utilized in the instant application. Thus, Trill et al teach the utilization of two vectors that the same amplifiable marker, DHFR, and are amplified by the same agent, (please see page 556 table experiment 1 in particular). Trill et al also teach that high-level expression can be achieved by initial selection and subsequent amplification, co-amplification using different amplifiable markers, and initial selection and amplification en masse followed by dilution cloning to identify the clones expressing at high levels thus leading to a hybrid cell comprising the heavy and light chain of the desired antibody (please see discussion, page 556 2nd column, in particular), thus inherently teaching the culturing of the recombinant cells comprising the polynucleotides. Trill et al also teach that suspension cells also offer more flexibility in terms of the size and processors of the bioreactors and hence using NSO cell have reported a three- fourfold increase in expression (page 558, 1st column, in particular). Trill also teach that the amplifiable markers can be selected from glutamine synthetase, adenosine deaminase, DHFR (page 555 column 2, in particular); and as Orlandi et al evidences that antibodies are produced by B cells or B lymphocytes (please see entire article) in addition to teachings the methods for obtaining the nucleic acid sequences of the heavy and light chains using PCR methodologies.

Thus, Trill et al teach the production of a human antibody by fusing two myeloma cells, wherein the first myeloma cell comprises a heavy chain expression vector comprising an amplifiable marker and the second myeloma cell comprises a light chain expression vector comprising an amplifiable marker, wherein the amplifiable markers can be selected from glutamine synthetase, adenosine deaminase, DHFR. Thus, the

recovery of the antibody from the hybrid cell, even though not spelled out, is inherently involved in the process of production of the antibodies by fusing the two myeloma cells (please see the entire article in particular). In addition, Trill et al teaches that using NSO cell have reported a three- fourfold increase in expression. Further, Trill et al also teach the methods (page 556 2nd column in particular) wherein the first and second cells expressing the desired heavy and light chains "initial selection and subsequent amplification of candidate colonies" which inherently read on claims 34-37.

Thus, Trill et al anticipate claims 24, 25, 27-32 and 34-38 evidenced by Orlandi et al.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 24-38 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 5-8 of U.S. Patent No. 6,677,138 in view of Trill et al (Current Opinion in Biotechnology. 1995. 6:553-560; IDS – 06/22/2006) as evidenced by Orlandi et al (Proc. Natl. Acad. Sci. USA, 86:3833-3837, 1989).

Claims 24, 25, 27-32 and 34-38 are described supra. Further, claims 26 and 33 are drawn to the method wherein the first cell expresses an irrelevant light chain and expresses the desired heavy chain prior to fusion with the second cell.

Claims 1-8 of U.S. Patent No. 6,677,138 are drawn to a method for producing an antibody, said method comprising: (a) introducing an expression vector comprising a nucleotide sequence encoding a heavy chain into a first NS0-bc12 host cell; (b) introducing an expression vector comprising a nucleotide sequence encoding a light chain into a second NS0-bc12 host cell; and (c) fusing the first and second cells to form a hybrid cell, wherein the hybrid cell expresses an antibody comprised of the heavy chain and the light chain (d) culturing the hybrid cells so as to express the antibody; and (e) recovering the antibody from the hybrid cell culture, wherein the first NS0-bc12 host cell expresses both an irrelevant light chain and the heavy chain prior to fusion with the second NS0-bc12 host cell, wherein the antibody is expressed only after fusion of said first and second NS0-bc12 host cells, wherein the first NS0-bc12 host cell expressing the heavy chain is further selected for based on its rate of antibody production, wherein both the second NS0-bc12 host cell expressing the light chain and the first NS0-bc12

host cell expressing the heavy chain are each further selected for based on their rate of antibody production, wherein the antibody is a human antibody.

Trill has been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced the method for producing a human antibody as claimed by combining the teachings of Claims 1-8 of U.S. Patent No. 6,677,138 in view of Trill et al as evidenced by Orlandi et al for the reasons below.

One of ordinary skill in the art would have been motivated and would have reasonable expectation of success to have used the method as taught by Claims 1-8 of U.S. Patent No. 6,677,138, because Claims 1-8 of U.S. Patent No. 6,677,138 to a method for producing an antibody, said method comprising: (a) introducing an expression vector comprising a nucleotide sequence encoding a heavy chain into a first NS0-bc12 host cell; (b) introducing an expression vector comprising a nucleotide sequence encoding a light chain into a second NS0-bc12 host cell; and (c) fusing the first and second cells to form a hybrid cell, wherein the hybrid cell expresses an antibody comprised of the heavy chain and the light chain (d) culturing the hybrid cells so as to express the antibody; and (e) recovering the antibody from the hybrid cell culture, wherein the first NS0-bc12 host cell expresses both an irrelevant light chain and the heavy chain prior to fusion with the second NS0-bc12 host cell, wherein the antibody is expressed only after fusion of said first and second NS0-bc12 host cells,

wherein the first NS0-bc12 host cell expressing the heavy chain is further selected for based on its rate of antibody production, wherein both the second NS0-bc12 host cell expressing the light chain and the first NS0-bc12 host cell expressing the heavy chain are each further selected for based on their rate of antibody production, wherein the antibody is a human antibody.

In addition, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have come up with a method of producing a human antibody as claimed because Claims 1-8 of U.S. Patent No. 6,677,138 teach the same exact methods to produce a human antibody and combine with the teachings of Trill et al, because Trill et al teach the same method of production of genetically engineered human monoclonal antibodies in COS and CHO cells, vectors for the expression of mABs in COS and CHO cells wherein the amplifiable markers were "DHFR" for heavy chain and "neo" for light chain; in addition to teaching that there are numerous reports that describe the use of vector system in which the two Ig chains are situated in different plasmids containing independent amplifiable/selectable markers; in addition Trill et al also teach the utilization of two vectors that the same amplifiable marker, DHFR, and are amplified by the same agent, (please see page 556 table experiment 1 in particular).

Moreover, one of ordinary skill in the art would have known to combine the studies of Claims 1-8 of U.S. Patent No. 6,677,138 with Trill et al because Trill et al reveals the methods of selecting the cells desirable clones by teaching that high-level expression can be achieved by initial selection and subsequent amplification, co-

amplification using different amplifiable markers, and initial selection and amplification en masse followed by dilution cloning to identify the clones expressing at high levels thus leading to a hybrid cell comprising the heavy and light chain of the desired antibody (please see discussion, page 556 2nd column, in particular), thus inherently teaching the culturing of the recombinant cells comprising the polynucleotides. Trill et al also teach that suspension cells also offer more flexibility in terms of the size and processors of the bioreactors and hence using NSO cell have reported a three- fourfold increase in expression (page 558, 1st column, in particular). Trill also teach that the amplifiable markers can be selected from glutamine synthetase, adenosine deaminase, DHFR (page 555 column 2, in particular); and as Orlandi et al evidences that antibodies are produced by B cells or B lymphocytes (please see entire article) in addition to teachings the methods for obtaining the nucleic acid sequences of the heavy and light chains using PCR methodologies.

Thus, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have produced the claimed method because both Claims 1-8 of U.S. Patent No. 6,677,138 and Trill et al combined teach the method as claimed wherein a human antibody is produced by fusing two myeloma cells, wherein the first myeloma cell comprises a heavy chain expression vector comprising an amplifiable marker and the second myeloma cell comprises a light chain expression vector comprising an amplifiable marker, wherein the amplifiable markers can be selected from glutamine synthetase, adenosine deaminase, DHFR. In addition, Trill et al teaches that using NSO cell have reported a three- fourfold increase in

expression. Further, Trill et al also teach the methods (page 556 2nd column in particular) wherein the first and second cells expressing the desired heavy and light chains "initial selection and subsequent amplification of candidate colonies" which read on claims 34-37, in addition to Trill et al also teach the utilization of two vectors that the same amplifiable marker, DHFR, and are amplified by the same agent.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

9. Claims 24-38 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 6-13 and 15-27 of U.S. Patent No. 6,420,140 in view of Trill et al (Current Opinion in Biotechnology. 1995. 6:553-560; IDS – 06/22/2006).

The instant claims have been described supra.

Claims 1-4, 6-13 and 15-27 of U.S. Patent No. 6,420,140 are drawn to a method for producing an antibody, said method comprising: a) introducing an expression vector comprising a nucleotide sequence encoding a heavy chain into a first mammalian, non-lymphoid host cell; (b) introducing an expression vector comprising a nucleotide sequence encoding a light chain into a second mammalian, non-lymphoid host cell; and (c) fusing the first and second cells to form a hybrid cell, wherein the hybrid cell expresses an antibody comprised of the heavy chain and the light chain,: (d) culturing the hybrid cells so as to express the antibody; and (e) recovering the antibody from the

hybrid cell culture, wherein the nucleotide sequence encoding a heavy chain and the nucleotide sequence encoding a light chain are each obtained from a B-cell or a hybridoma cell, wherein said B-cell or hybridoma cell produce an antibody, wherein the first cell expresses both an irrelevant light chain and the heavy chain prior to fusion with the second cell, wherein the antibody is expressed only after fusion of said first and second mammalian cells, wherein the first cell expressing the heavy chain is further selected for based on its rate of antibody production, wherein both the second cell expressing the light chain and the first cell expressing the heavy chain are each further selected for based on their rate of production, wherein the antibody is a human antibody. The claims are further drawn to a method for producing an antibody, said method comprising: (a) introducing an expression vector comprising a nucleotide sequence encoding a heavy chain into a first myeloma host cell; (b) introducing an expression vector comprising a nucleotide sequence encoding a light chain into a second myeloma host cell; and (c) fusing the first and second cells to form a hybrid cell, wherein the hybrid cell expresses an antibody comprised of the heavy chain and the light chain (d) culturing the hybrid cells so as to express the antibody; and (e) recovering the antibody from the hybrid cell culture, wherein the nucleotide sequence encoding a heavy chain and the nucleotide sequence encoding a light chain are each obtained from a B-cell or a hybridoma cell, wherein said B-cell or hybridoma cell produce an antibody, wherein the first cell expresses both an irrelevant light chain and the heavy chain prior to fusion with the second cell, wherein the antibody is expressed only after fusion of said first and second mammalian cells, wherein the first cell expressing the heavy chain

is further selected for based on its rate of antibody production, wherein both the second cell expressing the light chain and the first cell expressing the heavy chain are each further selected for based on their rate of production, wherein the antibody is a human antibody. In addition, the claims are drawn to a method for producing an antibody, said method comprising: (a) introducing an expression vector comprising a nucleotide sequence encoding a heavy chain into a first NS0 host cell; (b) introducing an expression vector comprising a nucleotide sequence encoding a light chain into a second NS0 host cell; and (c) fusing the first and second cells to form a hybrid cell, wherein the hybrid cell expresses an antibody comprised of the heavy chain and the light chain (d) culturing the hybrid cells so as to express the antibody; and (e) recovering the antibody from the hybrid cell culture, wherein the nucleotide sequence encoding a heavy chain and the nucleotide sequence encoding a light chain are each obtained from a B-cell or a hybridoma cell, wherein said B-cell or hybridoma cell produce an antibody, wherein the first cell expresses both an irrelevant light chain and the heavy chain prior to fusion with the second cell, wherein the expression of the heavy chain by the first cell is determined by ELISA analysis of lysate from the first cell, wherein the antibody is expressed only after fusion of said first and second mammalian cells, wherein the first cell expressing the heavy chain is further selected for based on its rate of antibody production, wherein both the second cell expressing the light chain and the first cell expressing the heavy chain are each further selected for based on their rate of production, wherein the antibody is a human antibody.

Trill has been described supra

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced the method for producing a human antibody as claimed by combining the teachings of Claims 1-4, 6-13 and 15-27 of U.S. Patent No. 6,420,140 in view of Trill et al.

One of ordinary skill in the art would have been motivated and would have reasonable expectation of success to have used the method as taught by Claims 1-4, 6-13 and 15-27 of U.S. Patent No. 6,420,140, because Claims 1-4, 6-13 and 15-27 of U.S. Patent No. 6,420,140 are drawn to a method for producing an antibody, said method comprising: a) introducing an expression vector comprising a nucleotide sequence encoding a heavy chain into a first mammalian, non-lymphoid host cell; (b) introducing an expression vector comprising a nucleotide sequence encoding a light chain into a second mammalian, non-lymphoid host cell; and (c) fusing the first and second cells to form a hybrid cell, wherein the hybrid cell expresses an antibody comprised of the heavy chain and the light chain,: (d) culturing the hybrid cells so as to express the antibody; and (e) recovering the antibody from the hybrid cell culture, wherein the nucleotide sequence encoding a heavy chain and the nucleotide sequence encoding a light chain are each obtained from a B-cell or a hybridoma cell, wherein said B-cell or hybridoma cell produce an antibody, wherein the first cell expresses both an irrelevant light chain and the heavy chain prior to fusion with the second cell, wherein the antibody is expressed only after fusion of said first and second mammalian cells,

wherein the first cell expressing the heavy chain is further selected for based on its rate of antibody production, wherein both the second cell expressing the light chain and the first cell expressing the heavy chain are each further selected for based on their rate of production, wherein the antibody is a human antibody. The claims are further drawn to a method for producing an antibody, said method comprising: (a) introducing an expression vector comprising a nucleotide sequence encoding a heavy chain into a first myeloma host cell; (b) introducing an expression vector comprising a nucleotide sequence encoding a light chain into a second myeloma host cell; and (c) fusing the first and second cells to form a hybrid cell, wherein the hybrid cell expresses an antibody comprised of the heavy chain and the light chain (d) culturing the hybrid cells so as to express the antibody; and (e) recovering the antibody from the hybrid cell culture, wherein the nucleotide sequence encoding a heavy chain and the nucleotide sequence encoding a light chain are each obtained from a B-cell or a hybridoma cell, wherein said B-cell or hybridoma cell produce an antibody, wherein the first cell expresses both an irrelevant light chain and the heavy chain prior to fusion with the second cell, wherein the antibody is expressed only after fusion of said first and second mammalian cells, wherein the first cell expressing the heavy chain is further selected for based on its rate of antibody production, wherein both the second cell expressing the light chain and the first cell expressing the heavy chain are each further selected for based on their rate of production, wherein the antibody is a human antibody. In addition, the claims are drawn to a method for producing an antibody, said method comprising: (a) introducing an expression vector comprising a nucleotide sequence encoding a heavy chain into a first

NS0 host cell; (b) introducing an expression vector comprising a nucleotide sequence encoding a light chain into a second NS0 host cell; and (c) fusing the first and second cells to form a hybrid cell, wherein the hybrid cell expresses an antibody comprised of the heavy chain and the light chain (d) culturing the hybrid cells so as to express the antibody; and (e) recovering the antibody from the hybrid cell culture, wherein the nucleotide sequence encoding a heavy chain and the nucleotide sequence encoding a light chain are each obtained from a B-cell or a hybridoma cell, wherein said B-cell or hybridoma cell produce an antibody, wherein the first cell expresses both an irrelevant light chain and the heavy chain prior to fusion with the second cell, wherein the expression of the heavy chain by the first cell is determined by ELISA analysis of lysate from the first cell, wherein the antibody is expressed only after fusion of said first and second mammalian cells, wherein the first cell expressing the heavy chain is further selected for based on its rate of antibody production, wherein both the second cell expressing the light chain and the first cell expressing the heavy chain are each further selected for based on their rate of production, wherein the antibody is a human antibody.

In addition, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have come up with a method of producing a human antibody as claimed because Claims 1-4, 6-13 and 15-27 of U.S. Patent No. 6,420,140 teach the same exact methods to produce a human antibody and combine with the teachings of Trill et al, because Trill et al teach the same method of production of genetically engineered human monoclonal antibodies in COS and CHO

cells, vectors for the expression of mABs in COS and CHO cells wherein the amplifiable markers were "DHFR" for heavy chain and "neo" for light chain; in addition to teaching that there are numerous reports that describe the use of vector system in which the two Ig chains are situated in different plasmids containing independent amplifiable/selectable markers, further teachings that the utilization of two vectors that the same amplifiable marker, DHFR, and are amplified by the same agent.

Moreover, one of ordinary skill in the art would have known to combine the studies of Claims 1-4, 6-13 and 15-27 of U.S. Patent No. 6,420,140 with Trill et al because Trill et al reveals the methods of selecting the cells desirable clones by teaching that high-level expression can be achieved by initial selection and subsequent amplification, co-amplification using different amplifiable markers, and initial selection and amplification en masse followed by dilution cloning to identify the clones expressing at high levels thus leading to a hybrid cell comprising the heavy and light chain of the desired antibody (please see discussion, page 556 2nd column, in particular), thus inherently teaching the culturing of the recombinant cells comprising the polynucleotides. Trill et al also teach that suspension cells also offer more flexibility in terms of the size and processors of the bioreactors and hence using NSO cell have reported a three- fourfold increase in expression (page 558, 1st column, in particular). Trill also teach that the amplifiable markers can be selected from glutamine synthetase, adenosine deaminase, DHFR (page 555 column 2, in particular.

Thus, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have produced the claimed method

because both Claims 1-4, 6-13 and 15-27 of U.S. Patent No. 6,420,140 and Trill et al combined teach the method as claimed wherein a human antibody is produced by fusing two myeloma cells, wherein the first myeloma cell comprises a heavy chain expression vector comprising an amplifiable marker and the second myeloma cell comprises a light chain expression vector comprising an amplifiable marker, wherein the amplifiable markers can be selected from glutamine synthetase, adenosine deaminase, DHFR. In addition, Trill et al teaches that using NSO cell have reported a three- fourfold increase in expression. Further, Trill et al also teach the methods (page 556 2nd column in particular) wherein the first and second cells expressing the desired heavy and light chains "initial selection and subsequent amplification of candidate colonies" which read on claims 34-37.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

10. Claims 24-38 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-4, and 6-11 of U.S. Patent No. 6,207,418 in view of Trill et al (Current Opinion in Biotechnology. 1995. 6:553-560; IDS – 06/22/2006).

The instant claims have been described supra.

Claims 1-4, and 6-11 of U.S. Patent No. 6,207,418 are drawn to a method for producing a human antibody, said method comprising: (a) introducing an expression

vector comprising a nucleotide sequence encoding a human heavy chain polypeptide into a first mammalian host cell; (b) introducing an expression vector comprising a nucleotide sequence encoding a human light chain polypeptide into a second mammalian host cell; and (c) fusing the first and second cells to form a hybrid cell, wherein the hybrid cell expresses a human antibody comprised of the human heavy chain polypeptide and the human light chain polypeptide (d) culturing the hybrid cells so as to express the human antibody; and (e) recovering the human antibody from the hybrid cell culture, wherein the nucleotide sequence encoding a human heavy chain polypeptide and the nucleotide sequence encoding a human light chain polypeptide are each obtained from a B-cell or a hybridoma cell, wherein said B-cell or hybridoma cell produces a human antibody, wherein the first cell expresses both an irrelevant light chain and the human heavy chain polypeptide prior to fusion with the second cell, wherein the human antibody is expressed only after fusion of said first and second mammalian cells, wherein the first cell expressing the heavy chain is further selected for based on its rate of antibody production, wherein both the second cell expressing the light chain and the first cell expressing the heavy chain are each further selected for based on their rate of production. The claims are further drawn to a method for producing a human antibody, comprising: (a) introducing an expression vector comprising a nucleotide sequence encoding a human heavy chain polypeptide into a first mammalian host cell, wherein the first cell expresses an irrelevant light chain; (b) introducing an expression vector comprising a nucleotide sequence encoding a human light chain polypeptide into a second mammalian host cell; and (c) fusing the first and

second cells to form a hybrid cell, wherein the hybrid cell expresses a human antibody comprised of the human heavy chain polypeptide encoded by the introduced nucleotide sequence and the human light chain polypeptide encoded by the sequence introduced in the second cell; (d) culturing the hybrid cells so as to express the human antibody; (e) recovering the human antibody from the hybrid cell culture, wherein the irrelevant light chain in the first cell is present in an episomal vector.

Trill has been described supra

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced the method for producing a human antibody as claimed by combining the teachings of Claims 1-4, and 6-11 of U.S. Patent No. 6,207,418 in view of Trill et al.

One of ordinary skill in the art would have been motivated and would have reasonable expectation of success to have used the method as taught by Claims 1-4, and 6-11 of U.S. Patent No. 6,207,418 because Claims 1-4, and 6-11 of U.S. Patent No. 6,207,418 are drawn to a method for producing a human antibody, said method comprising: (a) introducing an expression vector comprising a nucleotide sequence encoding a human heavy chain polypeptide into a first mammalian host cell; (b) introducing an expression vector comprising a nucleotide sequence encoding a human light chain polypeptide into a second mammalian host cell; and (c) fusing the first and second cells to form a hybrid cell, wherein the hybrid cell expresses a human antibody

comprised of the human heavy chain polypeptide and the human light chain polypeptide (d) culturing the hybrid cells so as to express the human antibody; and (e) recovering the human antibody from the hybrid cell culture, wherein the nucleotide sequence encoding a human heavy chain polypeptide and the nucleotide sequence encoding a human light chain polypeptide are each obtained from a B-cell or a hybridoma cell, wherein said B-cell or hybridoma cell produces a human antibody, wherein the first cell expresses both an irrelevant light chain and the human heavy chain polypeptide prior to fusion with the second cell, wherein the human antibody is expressed only after fusion of said first and second mammalian cells, wherein the first cell expressing the heavy chain is further selected for based on its rate of antibody production, wherein both the second cell expressing the light chain and the first cell expressing the heavy chain are each further selected for based on their rate of production. The claims are further drawn to a method for producing a human antibody, comprising: (a) introducing an expression vector comprising a nucleotide sequence encoding a human heavy chain polypeptide into a first mammalian host cell, wherein the first cell expresses an irrelevant light chain; (b) introducing an expression vector comprising a nucleotide sequence encoding a human light chain polypeptide into a second mammalian host cell; and (c) fusing the first and second cells to form a hybrid cell, wherein the hybrid cell expresses a human antibody comprised of the human heavy chain polypeptide encoded by the introduced nucleotide sequence and the human light chain polypeptide encoded by the sequence introduced in the second cell; (d) culturing the hybrid cells so as to

express the human antibody; (e) recovering the human antibody from the hybrid cell culture, wherein the irrelevant light chain in the first cell is present in an episomal vector.

In addition, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have come up with a method of producing a human antibody as claimed because Claims 1-4, and 6-11 of U.S. Patent No. 6,207,418 teach the same exact methods to produce a human antibody and combine with the teachings of Trill et al, because Trill et al teach the same method of production of genetically engineered human monoclonal antibodies in COS and CHO cells, vectors for the expression of mABs in COS and CHO cells wherein the amplifiable markers were "DHFR" for heavy chain and "neo" for light chain; in addition to teaching that there are numerous reports that describe the use of vector system in which the two Ig chains are situated in different plasmids containing independent amplifiable/selectable markers.

Moreover, one of ordinary skill in the art would have known to combine the studies of Claims 1-4, and 6-11 of U.S. Patent No. 6,207,418 with Trill et al because Trill et al reveals the methods of selecting the cells desirable clones by teaching that high-level expression can be achieved by initial selection and subsequent amplification, co-amplification using different amplifiable markers, and initial selection and amplification en masse followed by dilution cloning to identify the clones expressing at high levels thus leading to a hybrid cell comprising the heavy and light chain of the desired antibody (please see discussion, page 556 2nd column, in particular), thus inherently teaching the culturing of the recombinant cells comprising the polynucleotides. Trill et al also teach

that suspension cells also offer more flexibility in terms of the size and processors of the bioreactors and hence using NSO cell have reported a three- fourfold increase in expression (page 558, 1st column, in particular). Trill also teach that the amplifiable markers can be selected from glutamine synthetase, adenosine deaminase, DHFR (page 555 column 2, in particular.

Thus, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have produced the claimed method because both Claims 1-4, 6-13 and 15-27 of U.S. Patent No. 6,420,140 and Trill et al combined teach the method as claimed wherein a human antibody is produced by fusing two myeloma cells, wherein the first myeloma cell comprises a heavy chain expression vector comprising an amplifiable marker and the second myeloma cell comprises a light chain expression vector comprising an amplifiable marker, wherein the amplifiable markers can be selected from glutamine synthetase, adenosine deaminase, DHFR. In addition, Trill et al teaches that using NSO cell have reported a three- fourfold increase in expression. Further, Trill et al also teach the methods (page 556 2nd column in particular) wherein the first and second cells expressing the desired heavy and light chains "initial selection and subsequent amplification of candidate colonies" which read on claims 34-37. In addition to teaching that there are numerous reports that describe the use of vector system in which the two Ig chains are situated in different plasmids containing independent amplifiable/selectable markers, further teachings that the utilization of two vectors that the same amplifiable marker, DHFR, and are amplified by the same agent.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

11. Claims 24-38 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-4, and 6-11 of U.S. Patent No. 5,916,771 in view of Trill et al (Current Opinion in Biotechnology. 1995. 6:553-560; IDS – 06/22/2006).

The instant claims have been described supra.

Claims 1-4, and 6-11 of U.S. Patent No. 5,916,771 are drawn to a method for producing a human antibody, said method comprising: (a) introducing an expression vector comprising a nucleotide sequence encoding a human heavy chain polypeptide into a first mammalian host cell; (b) introducing an expression vector comprising a nucleotide sequence encoding a human light chain polypeptide into a second mammalian host cell; and (c) fusing the first and second cells to form a hybrid cell, wherein the hybrid cell expresses a human antibody comprised of the human heavy chain polypeptide and the human light chain polypeptide (d) culturing the hybrid cells so as to express the human antibody; and (e) recovering the human antibody from the hybrid cell culture, wherein the nucleotide sequence encoding a human heavy chain polypeptide and the nucleotide sequence encoding a human light chain polypeptide are each obtained from a B-cell or a hybridoma cell, wherein said B-cell or hybridoma cell

produces a human antibody, wherein the first cell expresses both an irrelevant light chain and the human heavy chain polypeptide prior to fusion with the second cell, wherein the human antibody is expressed only after fusion of said first and second mammalian cells, wherein the first cell expressing the heavy chain is further selected for based on its rate of antibody production, wherein both the second cell expressing the light chain and the first cell expressing the heavy chain are each further selected for based on their rate of production. The claims are further drawn to a method for producing a human antibody, comprising: (a) introducing an expression vector comprising a nucleotide sequence encoding a human heavy chain polypeptide into a first mammalian host cell, wherein the first cell expresses an irrelevant light chain; (b) introducing an expression vector comprising a nucleotide sequence encoding a human light chain polypeptide into a second mammalian host cell; and (c) fusing the first and second cells to form a hybrid cell, wherein the hybrid cell expresses a human antibody comprised of the human heavy chain polypeptide encoded by the introduced nucleotide sequence and the human light chain polypeptide encoded by the sequence introduced in the second cell; (d) culturing the hybrid cells so as to express the human antibody; (e) recovering the human antibody from the hybrid cell culture, wherein the irrelevant light chain in the first cell is present in an episomal vector.

Trill has been described supra

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced the method for producing a

human antibody as claimed by combining the teachings of Claims 1-4, and 6-11 of U.S. Patent No. 5,916,771 in view of Trill et al.

One of ordinary skill in the art would have been motivated and would have reasonable expectation of success to have used the method as taught by Claims 1-4, and 6-11 of U.S. Patent No. 5,916,771 because Claims 1-4, and 6-11 of U.S. Patent No. 5,916,771 are drawn to a method for producing a human antibody, said method comprising: (a) introducing an expression vector comprising a nucleotide sequence encoding a human heavy chain polypeptide into a first mammalian host cell; (b) introducing an expression vector comprising a nucleotide sequence encoding a human light chain polypeptide into a second mammalian host cell; and (c) fusing the first and second cells to form a hybrid cell, wherein the hybrid cell expresses a human antibody comprised of the human heavy chain polypeptide and the human light chain polypeptide (d) culturing the hybrid cells so as to express the human antibody; and (e) recovering the human antibody from the hybrid cell culture, wherein the nucleotide sequence encoding a human heavy chain polypeptide and the nucleotide sequence encoding a human light chain polypeptide are each obtained from a B-cell or a hybridoma cell, wherein said B-cell or hybridoma cell produces a human antibody, wherein the first cell expresses both an irrelevant light chain and the human heavy chain polypeptide prior to fusion with the second cell, wherein the human antibody is expressed only after fusion of said first and second mammalian cells, wherein the first cell expressing the heavy chain is further selected for based on its rate of antibody production, wherein both the

second cell expressing the light chain and the first cell expressing the heavy chain are each further selected for based on their rate of production. The claims are further drawn to a method for producing a human antibody, comprising: (a) introducing an expression vector comprising a nucleotide sequence encoding a human heavy chain polypeptide into a first mammalian host cell, wherein the first cell expresses an irrelevant light chain; (b) introducing an expression vector comprising a nucleotide sequence encoding a human light chain polypeptide into a second mammalian host cell; and (c) fusing the first and second cells to form a hybrid cell, wherein the hybrid cell expresses a human antibody comprised of the human heavy chain polypeptide encoded by the introduced nucleotide sequence and the human light chain polypeptide encoded by the sequence introduced in the second cell; (d) culturing the hybrid cells so as to express the human antibody; (e) recovering the human antibody from the hybrid cell culture, wherein the irrelevant light chain in the first cell is present in an episomal vector.

In addition, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have come up with a method of producing a human antibody as claimed because Claims 1-4, and 6-11 of U.S. Patent No. 5,916,771 teach the same exact methods to produce a human antibody and combine with the teachings of Trill et al, because Trill et al teach the same method of production of genetically engineered human monoclonal antibodies in COS and CHO cells, vectors for the expression of mABs in COS and CHO cells wherein the amplifiable markers were "DHFR" for heavy chain and "neo" for light chain; in addition to teaching that there are numerous reports that describe the use of vector system in which the two

Ig chains are situated in different plasmids containing independent amplifiable/selectable markers, in addition to teaching that there are numerous reports that describe the use of vector system in which the two Ig chains are situated in different plasmids containing independent amplifiable/selectable markers, further teachings that the utilization of two vectors that the same amplifiable marker, DHFR, and are amplified by the same agent.

Moreover, one of ordinary skill in the art would have known to combine the studies of Claims 1-4, and 6-11 of U.S. Patent No. 5,916,771 with Trill et al because Trill et al reveals the methods of selecting the cells desirable clones by teaching that high-level expression can be achieved by initial selection and subsequent amplification, co-amplification using different amplifiable markers, and initial selection and amplification en masse followed by dilution cloning to identify the clones expressing at high levels thus leading to a hybrid cell comprising the heavy and light chain of the desired antibody (please see discussion, page 556 2nd column, in particular), thus inherently teaching the culturing of the recombinant cells comprising the polynucleotides. Trill et al also teach that suspension cells also offer more flexibility in terms of the size and processors of the bioreactors and hence using NSO cell have reported a three- fourfold increase in expression (page 558, 1st column, in particular). Trill also teach that the amplifiable markers can be selected from glutamine synthetase, adenosine deaminase, DHFR (page 555 column 2, in particular.

Thus, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have produced the claimed method

because both Claims 1-4, and 6-11 of U.S. Patent No. 5,916,771 and Trill et al combined teach the method as claimed wherein a human antibody is produced by fusing two myeloma cells, wherein the first myeloma cell comprises a heavy chain expression vector comprising an amplifiable marker and the second myeloma cell comprises a light chain expression vector comprising an amplifiable marker, wherein the amplifiable markers can be selected from glutamine synthetase, adenosine deaminase, DHFR. In addition to teaching that there are numerous reports that describe the use of vector system in which the two Ig chains are situated in different plasmids containing independent amplifiable/selectable markers, further teachings that the utilization of two vectors that the same amplifiable marker, DHFR, and are amplified by the same agent. Further, Trill et al teaches that using NSO cell have reported a three- fourfold increase in expression. Further, Trill et al also teach the methods (page 556 2nd column in particular) wherein the first and second cells expressing the desired heavy and light chains "initial selection and subsequent amplification of candidate colonies" which read on claims 34-37.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

12. Claim 24-38 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 50, 51, 56, 58-65, 67 and 69-74 of copending Application No. 10/155,839 (PGPUB 20030022291) in

view of Trill et al (Current Opinion in Biotechnology. 1995. 6:553-560; IDS – 06/22/2006).

This is a provisional obviousness-type double patenting rejection.

The instant claims have been described supra.

Claims 50, 51, 56, 58-65, 67 and 69-74 of copending Application No. 10/155,839 are drawn to a method for producing an antibody, said method comprising: (a) introducing a first polynucleotide into a first mammalian cell, wherein the first polynucleotide comprises & first amplifiable marker and a sequence encoding a heavy chain polypeptide of an antibody, wherein the first mammalian expresses an irrelevant light chain and said heavy chain polypeptide prior to fusion with a second mammalian cell (b) introducing a second polynucleotide into said second mammalian cell, wherein the second polynucleotide comprises a second amplifiable marker and a sequence encoding a light chain polypeptide of the antibody; (c) culturing each of said first and second cells separately in the presence of an amplification agent, wherein the first and second amplifiable markers are the same and are amplified by the same amplification aren't; and (d) fusing the cultured cells produced by steps (a)-(c) to form a hybrid cell, wherein the hybrid cell expresses the antibody, (e) recovering the antibody from the hybrid cells, wherein the first cells and the second cell are CHO cells, wherein the first and second amplifiable markers are each DHFR, glutamine synthetase, or adenosine deaminase, wherein the antibody is a human antibody. The claims are further drawn to a method comprising: (a) culturing a first recombinant mammalian myeloma cell in the

presence of a first amplification agent to produce a first amplified recombinant cell; wherein the first cell comprises a first polynucleotide comprising a first amplifiable marker and a sequence encoding a heavy chain polypeptide, wherein the first mammalian expresses an irrelevant light chain and said heavy chain polypeptide prior to fusion with a second mammalian cell (b) culturing said second recombinant mammalian myeloma cell in the presence of a second amplification agent to produce a second amplified recombinant cell; wherein the second cell comprises a second polynucleotide comprising a second amplifiable marker and a sequence encoding a light chain polypeptide, wherein the first and second amplifiable markers are amplified by the same amplification agent; and (c) fusing the first and second amplified recombinant mammalian myeloma cells to form a hybrid cells, wherein the hybrid cell expresses a human antibody; (d) recovering the antibody from the hybrid cell, wherein the first cell and the second cell are myeloma cell, non-lymphoid cells, NSO cells, CHO cells, wherein the polynucleotide encoding the heavy chain polypeptide and the polynucleotide encoding the light chain polypeptide are obtained from a B-cell or a hybridoma cell, wherein said B-cell or hybridoma cell produce an antibody, wherein the first and second cells expressing the desired heavy and light chains are selected for on or more desirable characteristics prior to fusing, wherein the desirable characteristic is a high production rate, and wherein the first and second amplifiable markers are each DHFR, glutamine synthetase, or adenosine deaminase, further wherein the antibody is a human antibody.

Trill has been described supra.

Thus, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have produced the claimed method because both Claims 50, 51, 56, 58-65, 67 and 69-74 of copending Application No. 10/155,839 and Trill et al (as descried above with all the limitations as claimed in the instant application) combined teach the method as claimed wherein a human antibody is produced by fusing two myeloma cells, wherein the first myeloma cell comprises a heavy chain expression vector comprising an amplifiable marker and the second myeloma cell comprises a light chain expression vector comprising an amplifiable marker, wherein the amplifiable markers can be selected from glutamine synthetase, adenosine deaminase, DHFR, in two different cell lines CHO and COS. In addition, Trill et al teaches that using NSO cell have reported a three- fourfold increase in expression.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

13. Claim 24, 25, 29 and 30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 38-40 of copending Application No. 10/353,844 (PGPUB 20040053363) in view of Trill et al (Current Opinion in Biotechnology. 1995. 6:553-560; IDS – 06/22/2006).

This is a provisional obviousness-type double patenting rejection.

Claims 38-40 of copending Application No. 10/353,844 teach a method for producing an antibody, said method comprising: fusing a first recombinant mammalian cell and a second recombinant mammalian cell to form a hybrid cell, wherein the first recombinant mammalian cell contains a first polynucleotide comprising a first amplifiable marker and a sequence encoding a heavy chain polypeptide, and wherein the second recombinant mammalian cell contains a second polynucleotide comprising a second amplifiable marker and a sequence encoding a light chain polypeptide; and culturing the hybrid cell in the presence of the amplification agent for the first and second amplifiable markers, wherein the first and second amplifiable markers are amplified by the same amplification agents; wherein the first and second recombinant not cultured in the presence of an amount of the amplification agent sufficient to provide for amplification of the first and second amplifiable marker prior to said fusing, recovering the antibody from the hybrid cell culture, wherein the first recombinant cell and the second recombinant cell are CHO cells.

Trill has been described supra.

Thus, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have produced the claimed method because both Claims 38-40 of copending Application No. 10/353,844 and Trill et al combined teach the method as claimed wherein a human antibody is produced by fusing two myeloma cells, wherein the first myeloma cell comprises a heavy chain expression vector comprising an amplifiable marker and the second myeloma cell

comprises a light chain expression vector comprising an amplifiable marker, wherein the amplifiable markers can be selected from glutamine synthetase, adenosine deaminase, DHFR, in two different cell lines CHO and COS.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

14. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

1. Fouser et al. 1992. Biotechnolopgy. 10:1121-1127.

2. Page et al. 1991. Biotechnology. 9:64-68.

3. Morrison et al. 1988. Clinical Chemistry. 34:1668-1675.

Conclusion

15. No claims are allowed

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

17. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
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Ph: (571) 272-8789

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER